Montana Compounding Pharmacy PC 5/9/18

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

May 9, 2018

Roy “Tim” G. Calcagno, R.Ph., Owner
Montana Compounding Pharmacy, P.C.
dba Montana Compounding Pharmacy and Wellness Center
111 N. Higgins Ave.
Missoula, Montana 59802-4494

Dear Mr. Calcagno:

From August 30, 2016, to September 20, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Montana Compounding Pharmacy, P.C. dba Montana Compounding Pharmacy and Wellness Center, located at 111 N. Higgins Ave., Missoula, Montana 59802. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a] for exemption from certain provisions of the FDCA. In addition, the investigators noted serious deficiencies in your practices for producing non-sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your firm on September 20, 2016. FDA acknowledges receipt of your facility’s response, dated October 9, 2016. Based on this inspection, it appears that you produced drug products that violate the FDCA.

A. Compounded Drug Products Under the FDCA

Section 503A of the FDCA describes the conditions under which human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505) [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 355(a)].[1] Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigators noted that drug products produced by your firm failed to meet one of the conditions of section 503A. Specifically, the investigators noted that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you distributed from January to March 2016. FDA has previously

notified your firm about its failure to meet this condition in our December 11, 2015, warning letter.

Therefore, you compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions in that section from the FDA approval requirement of section 505 of the FDCA, the requirement under section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the requirement of compliance with CGMP under section 501(a)(2)(B) of the FDCA. In the remainder of this letter, we refer to your drug products that do not qualify for exemptions under section 503A as the "ineligible drug products."

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigators noted that drug products were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed that:

1. Your firm used non-pharmaceutical grade drinking water, obtained from a bottled water dispenser located in the break room of your facility, in the production of non-sterile stock solutions and non-sterile drug products. Our investigators determined that the water was used in the production of dozens of drug products. During the inspection, our investigators collected a sample of the water obtained from the dispenser. FDA analysis of the **(b)(4)** identified the presence of *Burkholderia cepacia,* which is considered an objectionable microorganism.

2. Vermin was observed in the production facility by our investigator during the inspection. Specifically, a fly was observed in multiple areas of your production facility, including the area where components were being weighed, in the area where drug products were being formulated, and in the area where the formulations were being encapsulated. The fly was observed by our investigator making direct contact with your operator, a drug container, and work table during production.

3. Hazardous drugs were produced without providing adequate containment, segregation, or cleaning of work surfaces to prevent cross-contamination. Specifically, production of an estradiol drug product, formulated using a **(b)(4)** active pharmaceutical ingredient, was performed in the general pharmacy area with no controls in place to prevent cross-contamination with other products produced in the same general pharmacy area.

Furthermore, the manufacture of the ineligible drug products is subject to FDA's CGMP regulations, Title 21, Code of Federal Regulations (CFR), parts 210 and 211. The FDA investigators observed significant CGMP violations at your facility, causing the ineligible drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations included, for example:

1. Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(2)) and your firm failed to subject each lot of a component with potential for microbiological contamination that

is objectionable in view of its intended use to microbiological tests before use (21 CFR 211.84(d)(6)).

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

3. Your firm failed to adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(b)).

4. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Misbranded Drug Products

The ineligible drug products you compounded are intended for conditions not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses.[2]

Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. It is a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

D. Corrective Actions

We have reviewed your firm's response to the Form FDA 483, dated October 9, 2016.

Regarding the insanitary conditions observed during the inspection, some of your corrective actions appear to be adequate. However, we are unable to fully evaluate the following corrective action due to a lack of supporting documentation:

In your response, you stated that you have stopped using **(b)(4)** and "changed to **(b)(4)** for compounds." However, you did not provide any supporting documentation, such as an invoice and certificate of analysis. Furthermore, it is not clear how the **(b)(4)** will be handled or stored once opened.

The following corrective action appears to be deficient to address the insanitary condition noted:

Regarding our observation of producing hazardous drug products in the general pharmacy area, you indicated that your SOP's have been revised to read, "**(b)(4)**." However, you did not provide evidence that cleaning with **(b)(4)** is effective in decontaminating hazardous drug products. Furthermore, we remain concerned with the potential for cross-contamination due to the lack of controls for containing hazardous **(b)(4)** active pharmaceutical ingredients in the same area where non-hazardous drug products are produced.

For more information on compounding, please see FDA's website, at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A, including the condition on receipt of a prescription for an identified individual patient prior to compounding and distributing drug products.

In addition, regarding issues related to the conditions of section 503A of the FDCA, it appears that your firm has received valid prescriptions for individually-identified patients for the drug products you compounded and distributed after receipt of FDA's March 28, 2016, acknowledgement of your firm's warning letter response, in which we state that FDA will verify that you receive valid prescriptions for individually-identified patients for all of the compounded drug products that you produce, including compounded non-sterile drug products. However, should you resume compounding and distributing drug products that do not meet the conditions of section 503A, the compounding and distribution of such drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the drug CGMP regulations. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) and fully implement corrections that meet the minimum requirements of the CGMP regulations.[3]

In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. [*See* section 501 of the FDCA.] If you choose to contract with a laboratory to perform some functions required by CGMP, it is essential that you select a qualified contractor and that you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you introduce into interstate commerce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b)].

FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance materials, and systems. In particular, this review should assess your processing operations. A third party consultant with relevant manufacturing expertise should assist you in conducting this comprehensive evaluation.

E. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Please include an explanation of

each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction.

Your written notification should refer to the Warning Letter Number above (**521947**). Please address your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
United States Food and Drug Administration
19701 Fairchild Rd
Irvine, California 92612-2506

If you have questions regarding the contents of this letter, please contact Maria P. Kelly-Doggett, Compliance Officer, via email to maria.kelly-doggett@fda.hhs.gov or by phone at (425) 302-0427 and reference unique identifier **521947**.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

---

[1] We remind you that there are conditions other than those discussed in this letter that must be satisfied to qualify for the exemptions in section 503A of the FDCA. For example, another condition for the exemptions under section 503A of the FDCA is that the licensed pharmacist or licensed physician preparing it does not compound a drug product that appears on a list published by FDA at Title 21 CFR Part 216 of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (referred to as "the withdrawn or removed list") (section 503A(b)(1)(C)). During FDA's latest inspection, which occurred between August 30, 2016, and September 20, 2016, the investigators observed that your firm produced drug products containing phenylpropanolamine and drug products containing chloramphenicol. Please note that on October 7, 2016, FDA published a final rule amending its regulations at 21 CFR Part 216 to revise the withdrawn or removed list to include "all drug products containing phenylpropanolamine" and "all oral drug products containing chloramphenicol." 81 Fed. Reg. 69, 668. This final rule became effective on November 7, 2016. *Id.* Please be advised that if your firm currently compounds drug products containing phenylpropanolamine or oral drug products containing chloramphenicol, your firm is compounding drug products that do not meet the conditions of section 503A and are not eligible for the exemptions in that section.

[2] Your ineligible drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).

[3] In this letter, we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.